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10/796,298	03/09/2004	Masato Mitsuhashi	HITACH.055CP2	9108

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EXAMINER	
LU, FRANK WEI MIN	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/796,298	MITSUHASHI, MASATO	
	Examiner	Art Unit	
	Frank W. Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-75 and 77-214* is/are pending in the application.

4a) Of the above claim(s) *13,14,16-26,30-33,39-72,89,90 and 94-214* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,15,27-29,34-38,73-75,77-88 and 91-93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 February 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/04, 12/04, and 9/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 1, 3-38, 73-75 and 77-93, species (1) (the transfer of lysate to the oligo(dT)-immobilized plate comprises centrifugation, claims 12 and 88), species (6) (the mRNA quantified is cytokines, claims 28, 34, and 35), and species (9) (the mRNA of apoptosis genes involved in leukemia is quantified, claim 27) in the reply filed on October 23, 2006 is acknowledged. Therefore, claims 1-12, 15, 27-29, 34-38, 73-75, 77-88, and 91-93 will be examined.

Specification

2. The disclosure is objected to because of the following informality: note that pages 23 and 25 of the specification contain SEQ ID Nos: 23-28, 31-37, and 75-77 while the sequencing listing only contains SEQ ID Nos: 1-17. It is unclear why SEQ ID Nos: 23-28, 31-37, and 75-77 are not in the sequencing listing and why SEQ ID Nos: 1-17 is not in the specification.

Appropriate correction is required.

Claim Objections

3. Claim 6 is objected to because of the following informality: note that "PBT" is an abbreviation. It can only be used after the whole phrase representing "PBT" appears once.

4. Claim 80 is objected to because of the following informality: (1) "$1e^{10}$" should be "1×10^{10}"; and (2) "filterplate" should be "filter plate".

5. Claim 81 is objected to because of the following informality: (1) "$1e^5$ to $1e^{10}$" should be "10^5 to 10^{10}"; and (2) "filterplate" should be "filter plate".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-12, 15, 27-29, 34-38, 73-75, 77-88, and 91-93 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claim 1 is rejected as vague and indefinite. Since the claim does not indicate that a lysate comprising mRNA contains the specific mRNA, it is unclear how to quantify the specific mRNA. Please clarify.

9. Claim 4 or 78 is rejected as vague and indefinite because it is unclear how to filter whole blood if the whole blood is frozen prior to filtration. Please clarify.

10. Claim 27 is rejected as vague and indefinite. Since claims 1 and 27 do not indicate which apoptosis genes are involved in leukemia, it is unclear how the mRNA of apoptosis genes involved in leukemia is quantified. Furthermore, note that the specification does not indicate which apoptosis genes are involved in leukemia. Please clarify.

11. Claim 29 is rejected as vague and indefinite. Since claims 1 and 29 do not indicate what is a relationship between the quantification of mRNA and side effects of anti-cancer

drugs on white blood cells, it is unclear how the quantification of mRNA can be used to test side effects of anti-cancer drugs on white blood cells. Please clarify.

12. Claim 34 is rejected as vague and indefinite. Since there is no donor cell in claim 1, it is unclear how the mRNA of donor cell-mediated cytokines can be quantified. Please clarify.

13. Claim 35 is rejected as vague and indefinite. Since claims 1 and 35 do not indicate what is a relationship between the quantification of mRNA of donor cell-mediated cytokines and transplant rejection, it is unclear how the quantification of mRNA of donor cell-mediated cytokines can be used to test transplant rejection. Please clarify.

14. Claim 73 is rejected as vague and indefinite because it is unclear what means the phrase "the percent recovery of spiked control RNA" in step (g). Does this phrase mean the percent of spiked control RNA in the lysis buffer on the oligo(dT)-immobilized plate or mean something else? Furthermore, since steps (g) and (f) do not indicate what is a relationship between the percent recovery of spiked control RNA and the definite quantity of mRNA, it is unclear how to determine quantity of mRNA by applying the percent recovery of spiked control RNA. Please clarify.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claims 1, 3, 5, 8, 11, 12, 15, and 36-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ishikawa *et al.,* (Clinical Chemistry, 43, 764-770, 1997) in view of Mitsuhashi (WO 99/32654, published on July 1, 1999) and Garvin (US 2003/0170669 A1, priority date: April 11, 2000).

Regarding claims 1 and 3, Ishikawa *et al.,* teach collecting whole blood, administering an anticoagulant (ie., heparin) to the whole blood, removing erythrocytes and blood components other than leukocytes from the whole blood to yield leukocytes (ie., by centrifugation), lysing the leukocytes to produce a lysate comprising mRNA, transferring the lysate to an oligo(dT)-immobilized plate to capture the mRNA, and quantifying the specific mRNA (ie., by quantifying synthesized cDNA) as recited in steps (a) to (f) of claim 1 where heparin is administered to the whole blood prior to collection of leukocytes as recited in claim 3 (see page 765, right column, page 766, left column and last paragraph of right column).

Regarding claim 11, Ishikawa *et al.,* teach that the immobilized plate comprises a multi-well oligo(dT)-immobilized plate (see page 765, right column, last paragraph and page 766, left column, first paragraph).

Regarding claim 15, Ishikawa *et al.,* teach the quantification of mRNA comprises cDNA synthesis of the specific mRNA (ie., ODC mRNA) and amplification of resulting cDNA (see page 766).

Regarding claim 36, Ishikawa *et al.,* teach additionally comprising determining the quantity of target mRNA in the sample using spiked control RNA (ie., rabbit globin mRNA) (see page 766).

Regarding claim 37, Ishikawa *et al.,* teach additionally comprising application of specific antisense primers during said lysate transferring step (ie., hybridizing oligo(dT) on the GenePlate to the mRNA in said lysate wherein oligo(dT) can serve as a primer) (see page 765, right column, last paragraph and page 766, left column, first paragraph).

Regarding claim 38, Ishikawa *et al.,* teach additionally comprising application of specific antisense primers (ie., antisense primer in PCR reaction) during said mRNA quantification step (see page 766).

Ishikawa *et al.,* do not disclose removing erythrocytes and blood components other than leukocytes from the whole blood by filtration to yield leukocytes on a filter membrane and lysing the leukocytes on a filter membrane as recited in steps (c) and (d) of claim 1 wherein the filter membrane is attached to a multi-well filter plate as recited in claim 5, that the transfer of lysate to the oligo(dT)-immobilized plate comprises centrifugation as recited in claim 12. However, Ishikawa *et al.,* teach removing erythrocytes and blood components other than leukocytes from the whole blood by centrifugation to yield leukocytes and lysing the leukocytes in a lysis buffer (see page 765, right column).

Mitsuhashi teach yielding leukocytes on a filter membrane and lysing the leukocytes on a filter membrane as recited in steps (c) and (d) of claim 1 wherein the filter membrane is attached to a multi-well filter plate as recited in claim 5 and that the transfer of lysate to the oligo(dT)-immobilized plate comprises centrifugation as recited in claim 12 (see pages 7 and 8).

Garvin teaches removing erythrocytes and blood components other than leukocytes from the whole blood by filtration to yield leukocytes on a filter membrane as recited in step (c) of claim 1 (see page 1).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the methods recited in claims 1 and 5 by removing erythrocytes and blood components other than leukocytes from the whole blood by filtration to yield leukocytes on a filter membrane and lysing the leukocytes on a filter membrane wherein the filter membrane is attached to a multi-well filter plate in view of the prior art of Ishikawa *et al.,* Mitsuhashi, and Garvin. One having ordinary skill in the art would have been motivated to do so because Mitsuhashi suggests that "[B]y placing cells on a filter membrane evenly and passing a lysis buffer through the cell layer on the filter membrane without mechanical homogenization of the cells, it is possible to drastically simplify the preparation of cell lysate and significantly stabilize the yield of recovered cytosolic RNA" (see page 6, third paragraph) and the simple substitution of one kind of filter (ie., the filter such as glass fiber taught by Mitsuhashi) from another kind of filter (ie., the filter such as Leukotrap WB taught by Garvin) for removing erythrocytes and blood components other than leukocytes from the whole blood during the process for performing the methods recited in claims 1 and 5, in the absence of convincing evidence to the contrary, would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since the filter such as Leukotrap WB taught by Garvin is commercially available and has an ability to remove more than 99.9% of leucocytes from one unit of while blood (see page 1, [0006] and [0007]).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

17. Claims 6 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ishikawa *et al.,* Mitsuhashi and Garvin as applied to claims 1, 3, 5, 8, 11, 12, 15, and 36-38 above, and further in view of Pall (US Patent No. 4,923,620, published on May 8, 1990).

The teachings of Ishikawa *et al.,* Mitsuhashi and Garvin have been summarized previously, *supra.*

Ishikawa *et al.,* Mitsuhashi and Garvin do not disclose that the filter membrane is a PBT fibrous membrane as recited in claim 6 wherein the leukocytes are captured on a plurality of filter membranes layered together as recited in claim 7.

Pall teaches to use polyester PET for leukocyte depletion from blood (see abstract, column 19, lines 40-67, column 20, lines 1-20, and column 27, lines 22-28) and combine two, three or more layers of fiber to form an integral element for adsorption of a portion of the leukocytes (see column 22, lines 1-24).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the methods recited in claims 6 and 7 wherein the filter membrane is a PBT fibrous membrane and the leukocytes are captured on a plurality of filter membranes layered together in view of the prior art of Ishikawa *et al.,* Mitsuhashi, Garvin, and Pall. One having ordinary skill in the art would have been motivated to do so because comparing with other leukocyte depletion resins, polyester PBT is a preferred material since "it also lends itself to radiation grafting and to subsequent conversion into preformed elements of controlled pore size by hot pressing" (see column 19, lines 63-67 and column 20, lines 1-4) and the integral element formed by two, three or more layers of fiber would provide large portion of the fiber surface on which leukocytes are removed by adsorption (see column 22, lines 1-24), and the simple substitution of one kind of filter (ie., the filter such as Leukotrap WB taught by Garvin) from another kind of filter (ie., PET filter taught by Pall) for removing erythrocytes and blood components other than leukocytes from the whole blood during the process for performing the methods recited in claims 6 and 7, in the absence of convincing evidence to the contrary, would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the

prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

18. Claims 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ishikawa *et al.,* Mitsuhashi and Garvin as applied to claims 1, 3, 5, 8, 11, 12, 15, and 36-38 above, and further in view of Naef (US Patent No. 5,177,085, published on January 5, 1993).

The teachings of Ishikawa *et al.,* Mitsuhashi and Garvin have been summarized previously, *supra.*

Ishikawa *et al.,* Mitsuhashi and Garvin do not disclose washing the leukocytes on the filter membrane with hypotonic buffer to further remove erythrocytes and other blood components as recited in claim 8. Since Mitsuhashi teaches to vacuum aspirate the filter plate to trap cells onto membranes (see page 7, step 1), Mitsuhashi discloses drying the filter membrane as recited in claim 9.

Naef teaches to remove erythrocytes by hypotonic lysis (see column 8, third paragraph).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 8 by washing the leukocytes on the filter membrane with hypotonic buffer to further remove erythrocytes and other blood components in view of the prior art of Ishikawa *et al.,* Mitsuhashi, Garvin, and Naef. One having ordinary skill in the art would have been motivated to do so because the addition of hypotonic lysis into whole blood would remove erythrocytes from whole blood (see Naef, column 8, third paragraph). One

having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to wash the leukocytes on the filter membrane with hypotonic buffer to further remove erythrocytes and other blood components in view of the prior art of Ishikawa *et al.,* Mitsuhashi, Garvin, and Naef.

Double Patenting

19. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

20. Claims 1, 3, 4, and 8 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of copending Application No. 11/376,018. Although the conflicting claims are not identical, they are not patentably distinct from each other because an obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but examined claims in this instant application are not patentably distinct from the reference claims

because the examined claims are either anticipated by, or would have been obvious over, the reference claims. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969). Although claims 1, 3, 4, and 8 in this instant application are not identical to claims 1-5 of copending Application No. 11/376,018, claims 1-5 of copending Application No. 11/376,018 are directed to the same subject matter and fall entirely within the scope of claims 1, 3, 4, and 8 in this instant application because the content of copending Application No. 11/376,018 (for example, see page 19, [0090] of the specification) teaches step (b) of claim 1 of this instant application. In other words, claims 1, 3, 4, and 8 in this instant application are anticipated by claims 1-5 of copending Application No. 11/376,018.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

21. No claim is allowed.

22. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG

94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)272-0735.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

September 6, 2006

FRANK LU
PRIMARY EXAMINER